REMARKS

I. STATUS OF THE APPLICATION

Claims 1–28 were filed in the original application. In the Amendment and Response to Restriction Requirement mailed May 1, 2006, claims 1–12, 14, 21, and 26 – 28 were cancelled, claims 13, 16–19, and 22–23 were amended, and claims 29–45 were added. In the Response to Office Action mailed August 3, 2006 claim 29 was cancelled, and claims 13, 16, 18, 19, 22, 30, 31, 34, were amended. In the Amendment and Response to the Office Action mailed January 24, 2007 claims 13, 15–20, 22–25, and 30–45 are cancelled, and claims 46–90 are added. In the present Request for Continued Examination and Amendment and Response to Final Office Action of August 7, 2007, claims 63, 82 and 89 are amended, and claims 91-96 are added. Therefore, claims 46-96 are currently pending.

The Applicants submit that the present amendments to the claims add no new subject matter. With regard to currently amended claims 63, 82 and 89, "electrospray time-of-flight mass spectrometry" has been deleted, and appears in newly added dependent claims 91, 93 and 95. With regard to claims 92, 94 and 96, support may be found throughout the Specification at, for example, Table 8, pages 39-40.

The Applicants note that all amendments of claims are made without acquiescing to any of the Examiner's arguments or rejections, and solely for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),[1] and without waiving the right to prosecute the amended or cancelled claims (or similar claims) in the future.

In the Office Action of August 7, 2007 there are 5 rejections to the claims. The currently pending rejections are:

1 65 Fed. Reg. 54603 (Sept. 8, 2000).

1. Claims 46, 51-52, 54-65, 70-71, 73-85, 89-90 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Parson et al. (Int J Legal Med., Vol. 111, pp. 124-132, 1998) (hereinafter "Parson") in view of Aaserud et al. (Am Soc Spectrometry, Vol. 7, pp. 1266-1269, 1996.) (hereinafter "Aaserud").

2. Claims 53 and 72 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Parson in view of Aaserud as applied to claims 46, 51-52, 54-65, 70-71, 73-85, 89-90 and further in view of Oefner et al. (US 6,453,244) (hereinafter "Oefner").

3. Claims 87-88 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Parson in view of Aaserud as applied to claims 46, 51-52, 54-65, 70-71, 73-85, 89-90 and further in view of Howell et al. (Am J Hum Genet., Vol 66, pp. 1589-1598, 2000) (hereinafter "Howell").

4. Claims 47-50 and 66-69 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Parson in view of Aaserud as applied to claims 46, 51-52, 54-65, 70-71, 73-85, 89-90 and further in view of Torroni et al. (Genetics, Vol 144, pp. 1835-1850, 1996) (hereinafter "Torroni").

5. Claim 86 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Parson in view of Aaserud as applied to claims 46, 51-52, 54-65, 70-71, 73-85, 89-90 and further in view of Baumer (Am J Hum Genet., Vol 54, pp 618-630, 1994) (hereinafter "Baumer").

II. Rejections under 35 USC §103(a)

A *prima facie* case of obviousness requires the Examiner to cite to a reference which a) discloses all the elements of the claimed invention, b) suggests or motivates one of ordinary skill in the art to combine the claim elements to yield the claimed invention, and c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements negates a finding of a *prima facie* case and, without more, entitles the Applicants to allowance of the claims in issue. (MPEP)

The Applicants submit that: a) none of the references, alone or in combination, disclose all elements of the claimed invention; b) the rejection does not provide a suggestion or motivation to combine the elements to yield the claimed invention; and c) the combinations of references fail to provide a reasonable expectation of success should the combinations be carried out.

A. Parson in View of Aaserud

1. Missing elements in the Combination of Parson and Aaserud

In the Office Action of August 7, 2007 the Examiner argues:

> "It would have been prima facie obvious to a person of ordinary skill in the art at the time was made to modify the method of mtDNA analysis taught by Parson et al in a manner as taught by Aaserud et al. by incorporating measuring base-composition by mass spectrometry for the purpose of enhancing sensitivity of the method for analyzing sequence variations in said target nucleic acids." (Office Action of August 8, 2007, page 5).

The Applicants respectfully disagree. The Examiner's combination of Parson and Aaserud fails to teach or suggest the element "comparing said molecular masses of said

one or more amplification products with at least one database comprising a plurality of known molecular masses from said one or more segments of mitochondrial DNA from a plurality of subjects, thereby reaching a forensic conclusion" (claim 46). Moreover, the Examiner's combination of Parson and Aaserud fails to teach or suggest the element "comparing said base compositions of said one or more amplification products with at least one database comprising a plurality of known base compositions from said one or more segments of mitochondrial DNA from a plurality of subjects, thereby reaching a forensic conclusion" (claim 65). Similarly, the Examiner's combination of Parson plus Aaserud fails to teach or suggest the element "comparing base compositions of restriction fragments with at least one database comprising a plurality of known base compositions from one or more segments of mitochondrial DNA from a plurality of subjects, thereby reaching a forensic conclusion" (claim 69). Nor does the Examiner's combination of Parson plus Aaserud teach or suggest the element "determining the relative amounts of said one or more amplification products from the abundance of mass spectral peaks corresponding to said one or more amplification products" (claims 61 and 80). The Final Office Action of August 7, 2007 fails to point out where in Parson, Aaserud or in the combination of Parson plus Aaserud, these elements of the presently claimed invention are to be located.

In the present Amendment and Response to Final Office Action of August 7, 2007 the Applicants have added claims 91, 93 and 95 to read "wherein said mass spectrometry is electrospray time-of-flight mass spectrometry". Neither Parson nor Aaserud, or any of the other references of record teaches or suggests electrospray time-of-flight mass spectrometry. In view of the above, the Applicants respectfully request that this rejection be withdrawn.

As well, the Applicants have added claim 92 ("wherein said amplifying comprises polymerase chain reaction amplification with the purified oligonucleotide primer pair SEQ ID NO: 8 and SEQ ID NO: 9."), claim 94 ("wherein said amplifying comprises polymerase chain reaction amplification with the purified oligonucleotide primer pair SEQ ID NO: 18 and SEQ ID NO: 19.") and claim 96 ("wherein said amplifying comprises polymerase chain reaction amplification with the purified oligonucleotide

primer pair SEQ ID NO: 16 and SEQ ID NO: 17."). Neither Parson nor Aaserud teaches or suggests polymerase chain reaction amplification with the purified oligonucleotide primer pairs SEQ ID NO: 8 and SEQ ID NO: 9, SEQ ID NO: 18 and SED ID NO: 19, or SEQ ID NO: 16 and SEQ ID NO: 17. In view of the above, the Applicants respectfully request that this rejection be withdrawn.

In the Office Action of August 7, 2007 the Examiner argues:

> "With regard to claims 64, 83, Parson et al. teach that at least one database comprises a Federal Bureau of Investigation mitochondrial database (see page 125, col. 2, paragraph under Armed forces DNA identification laboratory, page 131, col. 1, paragraph 1 under case example." (Final Office Action of August 7, 2007, page 4.)

The Applicants respectfully disagree. The AFDIL database and the FBI mtDNA database are not the same. Contrary to the Examiner's assertion, Parson does not teach, suggest, or even mention the FBI mtDNA database. In view of the above, the Applicants respectfully request that this rejection be withdrawn.

2. The Examiner Provides no Motivation to Combine Parson and Aaserud

In the Office Action of August 7, 2007 the Examiner argues:

> "One skilled in the art would have been motivated to combine the method of analyzing mtDNA as taught by Parson et al. with a step determining molecular mass measurement by using mass spectrometry as taught by Aaserud et al. because the ordinary artisan would have a reasonable expectation of success that inclusion of said limitation would result in a sensitive comparison of base composition variations in mtDNA and accurate measurement of base compositions in said target because Aaserud et al explicitly taught that the mass spectrometry measures accurate molecular masses thereby providing correct base

compositions of a target nucleic acid (see abstract on page 1266) and such modification is considered as obvious over cited prior art." (Office Action of August 7, 2007, page 6).

The Applicants respectfully disagree. The Applicants note that Parson expressly teaches away from the presently claimed invention. The Parson reference is entitled:

"**Population data for 101 Austrian Caucasian mitochondrial DNA d-loop sequences: Application of mtDNA sequence analysis to a forensic case**" (Parson, page 124.) (Emphasis added.)

Accordingly, the entirety of the Parson reference characterizes mtDNA by sequence analysis.

To the contrary, claims 46, 65 and 84 of the presently claimed invention read:

"determining molecular masses of said plurality of amplification products by mass spectrometry, without sequencing said plurality of amplification products;"

As well, the "method of analyzing mtDNA as taught by Parson et al" (Final Office Action of August 7, 2007, page 5) (*i.e.*, mtDNA sequence analysis) expressly teaches away from the Aaserud reference. Aaserud analyzes synthetic DNA fragments by base composition derived from mass values, **not** by sequence analysis.

Hence, the **sequence analysis of Parson** teaches directly away from the **base composition analysis without sequencing** of the presently claimed invention, and teaches directly away from the **base composition analysis without sequencing** of Aaserud. Moreover, Aaserud does not teach, suggest or even mention forensic methods, or forensic applications. Nor does Aaserud teach, suggest or even mention mitochondrial DNA, or mitochondrial DNA heteroplasmy. In turn, Parson does not teach, suggest or even mention mass spectrometry, molecular mass analysis or analysis by base composition. Accordingly, the Applicants assert that the artisan of ordinary skill in

forensic methods of mtDNA analysis would have not made the rejection's combination of references.

The Applicants note that the Aaserud reference appeared in 1996 and the Parson reference appeared in 1998, both years before the filing date of the present application. Nevertheless, despite a long-felt and unmet need for improved forensic methods of mitochondrial DNA analysis as evidenced by multiple public and private mtDNA databases, no reference has been put forward by the Examiner that defeats the novelty and non-obviousness of the presently claimed invention. Nor has the Examiner provided evidence that one skilled in the art of analyzing mitochondrial DNA by the method of Parson (*i.e.*, sequencing) would have been motivated to combine Parson with Aaserud that teaches an opposite method (*i.e.*, no sequencing). In the Final Office Action of August 7, 2007 the Examiner has provided no evidence sustaining the Examiner's conjecture with regard to what an ordinary artisan would or would not have been motivated to do.

The Applicants further note that Parson describes multiple problems with sequencing as a method of analyzing mtDNA. See, for example:

> "Thus, some positions consistently show the same ambiguous results in one direction, although sequencing in the other direction the base call can clearly be made (e.g. 317, 324, 330). We consider these to be **problematic positions due to artifacts caused by sequencing chemistry** . . ." (Parson, page 129, column 1, first paragraph). (Emphasis added.)

> And:

> "While heteroplasmy was detected clearly in three instances in the present study, detection of unbalanced heteroplasmic mixtures by direct sequencing is **problematic due to sequence background**." (Parson, page 129, column 2, paragraph 1). (Emphasis added.)

And:

> "Polycytosine stretches occur in both hypervariable segments and are sometimes **problematic to interpret**. . . .The sequence following the C-stretch usually **cannot be analyzed properly** due to the sequence being "out of register" as the polymerase attempts to sequence through the different length variants (Fig. 3.)" (Parson, page 130, column 1, second paragraph). (Emphasis added.)

Despite explicit acknowledgement of these shortcomings (*i.e.*, unmet needs) in the method of mtDNA analysis of Parson, and the appearance of the Parson reference two years after the Aaserud reference, Parson et al. (*i.e.*, artisans of at least ordinary, if not extraordinary, skill in mtDNA analysis) did not arrive at the Examiner's combination. Rather, Parson describes bidirectional sequencing ("In such cases, unambiguous sequence information from one of the strands can be used to determine the correct base call." Parson, page 129, column 2, first paragraph), and sequencing of clones ("Once again, cloning experiments have been conducted to confirm heteroplasmic mixtures in the HV II C-stretch (data not shown) Parson, page 130, column 2, first paragraph) to rescue the method of analyzing mtDNA of Parson. Tellingly, at no point in Parson are alternative methods of mtDNA analysis taught, suggested, or even mentioned, let alone mass spectrometry, or base composition based on mass analysis without sequencing.

The Applicants respectfully note that the Examiner's references individually and collectively fail to teach or suggest making the Examiner's combination. Thus, the Examiner's references fail to establish *prima facie* obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

3. There is no Reasonable Expectation of Success in the Examiner's Combination of Parson and Aaserud

In the Office Action of August 7, 2007 the Examiner notes:

> "One skilled in the art would have been motivated to combine the method of analyzing mtDNA as taught by Parson et al. with a step determining base composition measurement by using mass spectrometry as taught by Aaserud et al. because the ordinary artisan would have a reasonable expectation of success that inclusion of said limitation would result in a sensitive comparison of base composition variations in mtDNA and accurate measurement of base compositions in said target because Aaserud et al explicitly taught that the mass spectrometry measures accurate molecular masses thereby providing correct base compositions of a target nucleic acid (see abstract on page 1266) and such modification is considered as obvious over cited prior art." (Office Action of August 7, 2007, page 6). (Emphasis added.)

To the contrary, Parson provides no instruction, teaching or suggestion to the ordinary artisan with regard to how to go about combining the inumerable combinations of Aaserud's methods without DNA sequencing, with Parson's method of mtDNA analysis with sequencing to arrive at the presently claimed invention. Alone and in combination, Parson and Aaserud fail to teach, suggest or instruct the artisan of ordinary skill how to go about selecting and operating components of the forensic methods of mitochondrial DNA analysis of the present application. Parson is silent. Aaserud is silent.

At no point in the Final Office Action of August 7, 2007 has the Examiner explained how an artisan of ordinary skill would have a reasonable expectation of success in arriving at the presently claimed invention in combining two methods, one for sequencing mtDNA, and one for not sequencing DNA. The Applicants note that such a hypothetical combination does not, and cannot, work. The method of Parson and the method of Aaserud are alternate, and divergent, methods of analysis.

In the Office Action of August 7, 2007 the Examiner has not advanced any evidence in support of the contention that the ordinary artisan using Parson's method of mtDNA analysis by sequencing and Aaserud's methods of synthetic ssDNA analysis

without sequencing, would have a reasonable expectation of success in arriving at the forensic methods of mitochondrial DNA analysis of the present application. Because the Examiner is not able to show that a reasonable expectation of success may be found in Parson plus Aaserud, the third prong of a prima facie case of obviousness is defective, as are prongs one and two.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

B. Parson in View of Aaserud and further in View of Oefner

The Applicants note that dependent claims 53 and 72 are not obvious for at least the same reasons that base claims 46 and 65 are not obvious. As discussed above (Section II.A.) the Applicants note that the Examiner's combination of Parson and Aaserud both individually, and in combination, fail to render claims 46 and 65 obvious. Oefner's description does not remedy the defects of the Examiner's combination of Parson and Aaserud. Thus, the Examiner's references fail to establish prima facie obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

C. Parson in View of Aaserud and further in View of Howard

The Applicants note that dependent claims 87 and 88 are not obvious for at least the same reasons that base claim 84 is not obvious. As discussed above (Section II.A.) the Applicants note that the Examiner's combination of Parson and Aaserud both individually, and in combination, fail to render claim 84 obvious. Howard's description does not remedy the defects of the Examiner's combination of Parson and Aaserud. Thus, the Examiner's references fail to establish prima facie obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

D. Parson in View of Aaserud and further in View of Torroni

The Applicants note that dependent claims 47-50 and 66-69 are not obvious for at least the same reasons that base claims 46 and 65 are not obvious. As discussed above (Section II.A.) the Applicants note that the Examiner's combination of Parson and Aaserud both individually, and in combination, fail to render claims 46 and 65 obvious. Torroni's description does not remedy the defects of the Examiner's combination of Parson and Aaserud. Thus, the Examiner's references fail to establish prima facie obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

E. Parson in View of Aaserud and further in View of Baumer

The Applicants note that dependent claim 86 is not obvious for at least the same reasons that base claim 84 is not obvious. As discussed above (Section II.A.) the Applicants note that the Examiner's combination of Parson and Aaserud both individually, and in combination, fail to render claim 84 obvious. Baumer's description does not remedy the defects of the Examiner's combination of Parson and Aaserud. Thus, the Examiner's references fail to establish prima facie obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of August 7, 2007 have been addressed, and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Dated: October 29, 2007

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